

## I. AMENDMENT

The following listing of claims replaces all prior versions and listings in the application:

### LISTING OF CLAIMS

1-32 (Canceled).

33. (Original) A wax-film composite comprised of a pH-sensitive mucoadhesive layer and a water-insoluble wax layer.

34. (Original) The wax-film composite of claim 33, wherein the pH-sensitive mucoadhesive layer is present at a concentration of 20% to 90% by weight, and the water-insoluble wax layer is present at a concentration of 10% to 80% by weight.

35. (Currently Amended) The wax-film composite of claim 33, wherein said pH-sensitive mucoadhesive ~~water-insoluble~~ layer is comprised of:

- at least one water-insoluble swellable mucoadhesive polymer,
- at least one pH-sensitive film-forming polymer, and
- at least one molecule of interest.

36. (Currently Amended) The wax-film composite of claim ~~[[33]]~~ 35, wherein the water-insoluble swellable mucoadhesive polymer is polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol.

37. (Currently Amended) The wax-film composite of claim ~~[[33]]~~ 35, wherein the water-insoluble swellable mucoadhesive polymer is Noveon or Carbomer.

38. (Currently Amended) The wax-film composite of claim ~~[[33]]~~ 35, wherein the water-insoluble swellable mucoadhesive polymer is present in the pH-sensitive mucoadhesive layer at a concentration from 0.1% to 20% by weight.

39 (Currently Amended) The wax-film composite of claim ~~[[33]]~~ 35, wherein the pH-sensitive film-forming polymer present in the pH-sensitive mucoadhesive layer is a copolymer of methacrylic acid and acrylic or methacrylic ester.

40. (Currently Amended) The wax-film composite of claim ~~[[33]]~~ 35, wherein the pH-sensitive film-forming polymer is present in the pH-sensitive mucoadhesive layer at a concentration ~~[[of]]~~ from 0.05% to 10% by weight.

41. (Currently Amended) The wax-film composite of claim ~~[[33]]~~ 35, wherein the pH-sensitive film-forming polymer present in the pH-sensitive mucoadhesive layer is a Eudragit polymer, or chemical derivative thereof.

42. (Original) The wax-film composite of claim 33, wherein the water-insoluble wax layer comprises at least one water-insoluble pharmaceutical wax having a melting point between 40° C and 100° C and at least one water-soluble or water-swellaable polymer.

43. (Original) The water-insoluble pharmaceutical wax of claim 42, wherein said wax is DENTSPLY® Utility Wax, beeswax, emulsifying wax, microcrystalline wax, carnauba wax, paraffin wax, white wax, yellow wax, or other suitable pharmaceutical wax.

44. (Currently Amended) The water-soluble or swellable polymer of claim 42, wherein said polymer is present in the insoluble wax layer at a concentration ~~[[of]]~~ from 0.05% to 10% by weight.

45. (Original) The water-soluble or swellable polymer of claim 42, wherein said water-soluble or water-swellaable polymer is tragacanth, polyvinyl, pyrrolidone, polyvinyl alcohol, cross-linked polyacrylic acid, polyethylene glycol, a cellulose polymer derivative, or other suitable pharmaceutical polymer that is water-soluble or water-swellaable.

46. (Currently Amended) The wax-film composite of claim [[33]] 35, wherein the molecule of interest is contained in and released from either the pH-sensitive mucoadhesive layer or the water-insoluble wax layer.

47. (Currently Amended) The wax-film composite of claim [[33]] 35, wherein the molecule of interest comprises an active pharmaceutical compound such as an antimicrobial, antiviral, antiinflammatory, antiseptic, antihistamine, a local anesthetic, a disinfectant, a keratolytic, an analgesic, an anti-migraine, anti-fungal, a sweetener, a flavoring agent, a diagnostic agent, or a combination thereof.

48. (Withdrawn) The wax-film composite of claim 33, wherein the molecule of interest is amlexanox.

49. (Withdrawn) The wax-film composite of claim 33, wherein the molecule of interest is triclosan.

50. (Withdrawn) The wax-film composite of claim 33, wherein the molecule of interest is lidocaine, benzocaine, or dyclonine.

51. (Currently Amended) The wax-film composite of claim [[33]] 35, wherein the molecule of interest is a peptide or protein.

52. (Withdrawn) The wax-film composite of claim 33, wherein the molecule of interest is at least one benzodiazepine drug or derivative thereof.

53. (Withdrawn) The wax-film composite of claim 33, wherein the molecule of interest is hirudin or hirudin complexed with a substance of opposite charge.

54. (Withdrawn) The wax-film composite of claim 53, wherein said substance of opposite charge is chitosan or protamine.

55. (Withdrawn) The wax-film composite of claim 33, wherein the molecule of interest is plasmid DNA or plasmid DNA complexed with a substance of opposite charge such as chitosan, protamine, or a cationic lipid.

56. (Currently Amended) The wax-film composite of claim 33, wherein the ~~application site is~~ wax-film composite is applied to an application site comprising: the skin, mouth, vagina, nasal cavity, or other accessible mucosal site.

57. (Currently Amended) The wax-film composite of claim [[33]] 56, wherein the wax-film composite adheres to the application site for at least one hour.

58. (Original) The wax-film composite of claim 33, wherein the wax-film composite has a total thickness of less than 5 mm.

59 - 62. (Canceled).

## II. RESPONSE TO OFFICE ACTION

### A. *Status of the Claims*

On January 5, 2004, per telephone conference between Mr. Barrett and Examiner Berko, species claim 51 was elected. Applicants confirm that election, without traverse.

Claims 33-58 were pending. Claims 48, 49, 50, and 52-55 are withdrawn. Claims 35-41, 44, 46, 47, 51, 56, and 57 have been amended. Therefore, claims 33-47, 52, 56, and 57 will be pending upon entry of these amendments.

### B. *Section 112, 2nd Paragraph Rejections*

Claim 46 stands rejected under 35. U.S.C. § 112, second paragraph, for lacking antecedent basis. Claim 46 has been amended to provide antecedent basis. Removal of the § 112 rejection is requested.

Claim 35 stands rejected under 35. U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office alleges that the limitation “and at least one molecule of interest” is indefinite because it does not specify the chemical nature of the molecule(s) or the number of such molecules involved. (Office Action, page 4). Applicants respectfully traverse.

The Office is obligated to judge the definiteness of the claims by reading them in light of the Specification. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986) (explaining that test for definiteness is whether “those skilled in the art would understand what is claimed when the claim is read in light of the specification”). When read in this manner, claim 35 is definite. The Specification explains that a molecule of interest is defined as:

...any synthetic or naturally occurring substance including elements, radioactive elements, synthetic or naturally small molecules, peptides, proteins, nucleic acids, or any combination thereof.

See Specification, page 12, fourth paragraph. Further, claim 35 recites the term “at least one,” which clearly defines the number of molecules required. In light of the clear explanation in the Specification of the molecules of interest as well as the definite recitation of the number of

molecules required in claim 35, Applicants submit that claim 35 is definite. For at least these reasons, Applicants respectfully request the removal of the § 112 rejection to claim 35.

Claims 46, 47, 51, 56, 57, and 58 also stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for improperly referring to claim 33 instead of claim 35. Claims 46, 47, 51, and 56 have been amended to properly depend from claim 35.

With respect to claims 57 and 58, Applicants respectfully traverse. Currently amended claim 57 recites: "The wax-film composite of claim 56, wherein the wax-film composite adheres to the application site for at least one hour." Claim 57, as amended, properly depends from amended claim 56, which introduces the application site limitation.

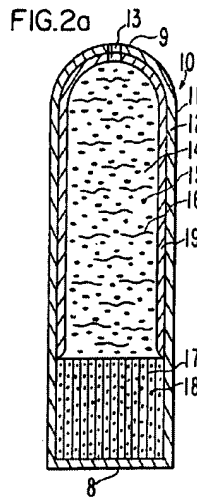
Applicants believe the rejection to claim 58 is erroneous. Claim 58 recites: "The wax-film composite of claim 33, wherein the wax-film composite has a total thickness of less than 5 mm." Claim 58 properly depends from claim 33, which recites a wax-film composite.

For at least the reasons set forth above, Applicants respectfully request the removal of the § 112 rejections to claims 46, 47, 51, 56, 57, and 58.

### *C. Section 102 Rejections*

Claims 1, 35, 37, and 56 stand rejected under 35 U.S.C. 102(a) as being anticipated by U.S. Patent No. 4,959,218 to Eckenhoff *et al.* Applicants believe that the reference to claim 1 is erroneous. In view of the comments below, Applicants respectfully traverse.

Independent claim 33 requires a wax-film composite, including a pH-sensitive mucoadhesive layer and a water-insoluble wax layer. *See* FIG. 1 and page 18, second paragraph of the present application for a non-limiting example. In contrast, the cited anticipation reference discloses an osmotic device used as a delivery medium to administer a medicament. (Column 2, lines 44-48). Referring to FIGS. 1 through 5 of the Eckenhoff reference, the device includes a body 11, a wall 12, exit means 13, a compartment 14, driving member 17, a liner 19, and a laminated coat 21.



Each of these fail to disclose a pH-sensitive *mucoadhesive* layer as required by claim 33. The present application defines mucoadhesive as:

...a substance that sticks or adheres to the skin or mucosal surfaces by force that are measureable and by any number of mechanisms such as, but not limited to the following: hydrogen-bonding, ionic interaction, hydrophobic interaction, van der Waals interaction, or combinations thereof.

See Specification, page 19, first paragraph. The cited reference fails to disclose that the device 10 adheres to any surface. In fact, the device is preferably designed for ease of *implantation* in a subcutaneous space. (Column 7, lines 15-16, emphasis added).

It is clear that the device of the cited anticipation reference does not disclose a wax-film composite including both a pH-sensitive mucoadhesive layer and a water-insoluble wax layer and the Office has failed to point to any evidence or passages indicating otherwise. If the Office disagrees, Applicants request citation to specific portions in the reference disclosing, for instance, a wax-film composite including both a pH-sensitive mucoadhesive layer and a water-insoluble wax layer.

For at least the reasons set forth above, claim 33, and all claims dependent therefrom, are not anticipated or otherwise rendered unpatentable, and the current rejection to claims 35, 37, and 56 should be withdrawn.

In addition, the cited anticipation reference fails to teach or suggest the limitations of dependent claims 35 and 37. For example, amended claim 35 recites, in part: "...said pH-sensitive mucoadhesive layer is comprised of: at least one water-insoluble swellable mucoadhesive polymer, at least one pH-sensitive film-forming polymer, and at least one molecule of interest." In addition, claim 37 recites in part "...wherein the water-insoluble swellable mucoadhesive polymer is Noveon or Carbomer." Ekenhoff does mention Carbopol or other water swellable polymers (Column 11, lines 25-60), however, these polymers are used to produce osmotic pressure in the Ekenhoff device and they are not used for mucoadhesion.

Further, the cited anticipation reference does not teach or suggest the limitations of amended claim 56 which recites, in part "...wherein the wax-film composite is applied to an application site comprising: the skin, mouth, vagina, nasal cavity, or other accessible mucosal site." As mentioned above, the cited reference does not teach or suggest the concept of mucoadhesion to adhere to an application site. The cited reference teaches an *implantable* osmotic device that is intended to release drugs at a controlled rate over a period of days or even months. (Column 3, lines 7-62, emphasis added).

Applicants also traverse the Office's stance that the cited anticipation reference teaches that the disclosed wax-film composite includes at least one medicament, e.g., anti-inflammatory compound, protein drug, and peptides. (Office Action, page 5). The cited anticipation reference does not teach a wax-film composite which comprises a pH-sensitive mucoadhesive layer and a water-insoluble wax layer as required by independent claim 33. Furthermore, the drug is not contained in either the osmopolymer compartment 18 or the wax-layer separating the osmopolymer compartment from the drug.

For at least the above reasons, Applicants respectfully request the removal of the §102 rejection.

C. *Section 103 Rejections*

Claims 34-47, 51, and 56-58 stand rejected under 35 U.S.C § 103(a) as being unpatentable over Ekenhoff *et al.* in view of U.S. Patent No. 5,700,478 to Biegajski *et al.* In view of the comments of this Response, Applicants respectfully traverse.



Rejected dependent claims 34-47, 51, and 56-58 are in condition for allowance for at least the reasons given above with respect to independent claim 33. Namely, the Eckenhoff reference does not disclose or suggest explicit elements required by claim 33.

Three basic criteria must be met to establish a *prima facie* case of obviousness:

- (1) there must be some suggestion or motivation, either in the References themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
- (2) there must be a reasonable expectation of success; and
- (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations.

*See* M.P.E.P. § 2142.

Here, the Office has not established a *prima facie* case, for it has not established any of these three criteria.

*1. The references, even when combined, do not teach or suggest all the claim limitations*

Even if the two cited references were combined, all of the present claim limitations would not be taught or even suggested.

Independent claim 33 recites, "A wax-film composite comprised of a pH-sensitive mucoadhesive layer and a *water-insoluble wax layer*." Such features are nowhere taught or suggested in the cited art, taken alone or in any combination.

As noted above, the Eckenhoff reference fails to teach or suggest all limitations of independent claim 33. However, combining the Eckenhoff reference with the Biegajski reference does not supply the above-noted features absent from the Eckenhoff reference. The laminate device disclosed in the Biegajski reference teaches that the mucoadhesive layer be fully comprised of water-soluble components. (*See* Column 3, lines 15-44; Column 5, lines 11-15; and Column 7, lines 7-10). Biegajski discloses that *all* layers of the laminate devices of the invention are water-soluble, and they therefore dissolve or disperse entirely in the fluids secreted within the body cavity. (Column 4, lines 57-60, emphasis added). Further, the Biegajski reference includes occluding layers constructed of a water-soluble polymer containing an additive such as silica gel or a wax. (Column 4, lines 35-38). Thus, the inclusion of an additive

such as a wax to a polymer layer does not make the layer a wax-layer. As such, the combination of the Eckenhoff reference and the Biegajski reference fails to teach or suggest every limitation cited in claim 33. For example, the water-insoluble wax layer is not disclosed or suggested even upon combination of the cited art.

Accordingly, none of the cited references teaches or even suggests the elements required by all the pending claims — particularly the pH-sensitive mucoadhesive layer and a water-insoluble wax layer. Thus, there can be no *prima facie* case of obviousness, and the pending claims are accordingly in condition for allowance.

2. *There is no suggestion or motivation to modify the references or to combine the reference teachings*

There is no motivation or suggestion in the references (or is cited by the Office) for the cited combination. Eckenhoff discloses a device comprising means for protecting a beneficial agent such as a drug from aqueous type fluids. (Column 2, lines 49-51). In particular, Eckenhoff provides a compartment 14 and a means 19, in which means 19 prevents external fluid from passing into the composition. (Column 6, lines 12-15). Eckenhoff teaches away from composites that may cause an infiltration of fluids to the composition. (Column 9, lines 56-67).

Further, such a combination would change the operation of Eckenhoff— instead of providing a device that prevents the passage of an external fluid that is present in the environment of use, Eckenhoff would hypothetically operate by first allowing a mucoadhesive layer to first fully dissolve when in contact with an aqueous solution and then prevent that aqueous solution from contaminating the composition. Accordingly, this combination is improper. *See* M.P.E.P. 2145 (X)(D)(2). (“It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). MPEP 2145 (X)(D)(2).”). The claims are therefore in condition for allowance.

3. *The Office has not established that there would be a reasonable expectation of success*

The Office has not shown or argued the required reasonable expectation of success. Applicants respectively submit that there is nothing in the cited art that demonstrates a reasonable expectation of success surrounding the combination of Eckenhoff and Biegajski as discussed above. In particular, there is nothing in the record to suggest that the layer of Biegajski in combination with the implantable device of Eckenhoff (and the significant operation-changing modifications that combination would entail) would be successful. Accordingly, for this reason as well, the claims are not *prima facie* obvious and should be allowed to issue.

For at least the reasons set forth above, claims 34-47, 51, and 56-58 are patentably distinct over the cited references. Applicants respectfully request the withdrawal of the § 103 rejection.

In addition, Applicants traverse the Office's stance that the use of Eudragit polymethacrylate copolymers and Carbopol 934 may be combined for making the adhesive layer for the drug deliver device and the wt% of polymer components. (Office Action, page 7). Biegajski does not teach or suggest, explicitly or implicitly, the use of Eudragit in combination with Carbopol 934 as a pH-sensitive mucoadhesive polymer to be contained in the adhesive layer. In fact, Biegajski teaches the use of Eudragit in a trilaminate film as the middle layer interposed between the adhesive layer and the drug-containing layer. (Column 22, lines 9-16 and Fig. 9). Biegajski teaches that the middle layer of the drug-containing layer does not contact a mucosal surface. (Column 33, lines 49-55).

The Office further rejects the invention, as a whole, as being *prima facie* obvious to one of ordinary skill in the art at the time it was made. (Office Action, page 8). Applicants respectfully traverse.

It appears that the Office is seeking to employ a conclusory statement that the recited features are *per se* obvious because, in the Office's unsupported opinion, those features are obvious design choices. Rejections of this type, based at most on impermissible hindsight, do not even approach a *prima facie* showing of obviousness. M.P.E.P. § 2143 (setting forth the requirements of a *prima facie* showing of obviousness). Accordingly, the current rejection cannot stand and should be removed to allow the pending claims to issue.

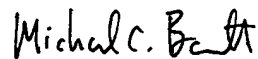
If this rejection is to be maintained, the Office's position must be supported by citing published references or by an Examiner's Affidavit sufficient to support the rejection, as required by M.P.E.P. § 2144.03. Specifically, Applicants request that the Office provide evidence and reasoning as to why one of skill in the art would find it obvious to make a wax-film composite including a pH-sensitive mucoadhesive layer and a water-insoluble wax layer.

### CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so the claims may swiftly pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3018 is respectfully requested in advance.

Respectfully submitted,



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